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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,300	TETZNER ET AL.	
	Examiner	Art Unit	
	Katherine Salmon	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/21/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, Claims 1-30 in the reply filed on 9/10/2007 is acknowledged.

2. Claims 1-31 are pending. Claim 31 is withdrawn as being drawn to a nonelected invention.

3. An action on the merits for Claims 1-30 is set forth below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-29 are indefinite because the claims do not recite the basic steps of the claimed method in a positive, active fashion. The claims are drawn to "detection of cytosine methylation ...characterized in that...the DNA to be investigated..is reacted..is amplified..is separated.." which are not active process steps. See Ex parte Erlich 3 USPQ2d, 1011 (BPAI 1986): "Method claims need not recite all operating details but should at least recite positive, active steps so that claim will set out and circumscribe particular area with reasonable degree of precision and particularly and make clear

what subject matter claims encompass, as well as make clear subject matter form which others would be precluded."

Claims 1-29 recite the limitation "the pretreated DNA" in step b line 1 of Claim 1. There is insufficient antecedent basis for this limitation in the claim. There is no pretreated DNA in step a. It is suggested that the claim be amended to incorporate pretreated DNA in step a in order to have antecedent basis.

Claims 1-29 recite the limitation "the primer extension product" in step c line 1 of Claim 1. There is insufficient antecedent basis for this limitation in the claim. There is no primer extension product in step a or b. It is suggested that the claim be amended to incorporate primer extension product in step a or b in order to have antecedent basis.

Claims 1-29 are indefinite over the phrase "is hereby characterized in that" in lines 1-2 of Claim 1. This phrase makes the metes and bounds of the claims unclear because it is not clear if the method is "consisting of", "consisting essentially of", or "comprising" steps a-e of Claim 1. It is noted that the claims are being interpreted broadly as "comprising" for the art rejections presented below.

Claims 1-29 are unclear over the phrase "at least one primer, whose 5'-end is joined with a probe via a linker (Scorpion primer)" in claim 1 line 7. The claims contain information in parentheses, i.e. (Scorpion primer). Parentheticals make the claim indefinite because it is unclear whether the information in the parentheses has the same, less, or more weight as the rest of the claim language.

Claim 2 is indefinite over the phrase "produced with a bisulfite" in line 2. It is unclear form the claim if the bisulfite is the chemical or enzyme that is reacted with the

DNA from step a of Claim 1 or it the "produced with a bisulfite" is a further step of step a.

Claim 3 is indefinite over the phrase "produced by means of a cytidine deaminase" in line 2. It is unclear form the claim if the cytidine deaminase is the chemical or enzyme that is reacted with the DNA from step a of Claim 1 or it the "produced by means of a cytidine deaminase" is a further step of step a.

Claim 3 is indefinite over the phrase "the unmethylated cytidine reacts more rapidly than methylated cytidine". This phrase is unclear because there are no cytidine (methylated or unmethylated) in claim 1. Further it is unclear if this limitation is a limitation of the claims because there is no active step.

Claim 6 is indefinite over the phrase "probe bears " because it is unclear what the metes and bounds of the phrase "probe bears" encompasses. It is not clear how the probe "bears" two signal components, if this phrase means the probe comprising two signal components or some other undefined relationship.

Claim 7 is unclear over the phrase "involve a quencher-fluorescent dye pair". It is not clear the metes and bounds of the phrase. It is not clear if the phrase means that the two signal comprises are a quencher-fluorescent dye pair or if these two signal components have some undefined relationship to the quencher-florescent dye pair.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board

of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 8 recites the broad recitation the secondary structure of the probe, and the claim also recites particularly by a hairpin shape which is the narrower statement of the range/limitation.

Claim 11-12 recites the limitation "the probe and another oligonucleotide" in line 2 of claim 11. There is insufficient antecedent basis for this limitation in the claim. It is suggested that the claim be amended to correct antecedent basis.

Claims 11-12 are indefinite over the phrase “each bears “ because it is unclear what the metes and bounds of the phrase “each bears” encompasses. It is not clear how the probe “bears” two signal components, if this phrase means the probe comprising two signal components or some other undefined relationship.

Claim 11-13 recites the limitation "the signal components" in line 3 of claim 11. There is insufficient antecedent basis for this limitation in the claim. It is suggested that the claim be amended to e.g. “the at least one signal component” to correct antecedent basis.

Claim 12 recites the limitation "the two signal components" in line 1-2. There is insufficient antecedent basis for this limitation in the claim. It is suggested that the claim be amended to e.g. "the at least one signal component" to correct antecedent basis.

Claim 13 recites the limitation "the spatial separation" in line 2. There is insufficient antecedent basis for this limitation in the claim. It is suggested that the claim be amended to e.g. "the probe and the another oligonucleotide are spatially separated" to correct antecedent basis.

Claim 13 is unclear over the phrased "assured by a duplex structure". It is unclear the metes and bounds of the phrased because it is not clear how inactive the probe and the other oligonucleotide must be to be "assured".

Claim 14-16 recites the limitation "the probe and another oligonucleotide" in line 2 of claim 14. There is insufficient antecedent basis for this limitation in the claim. It is suggested that the claim be amended to correct antecedent basis.

Claim 14-16 recites the limitation "the signal components" in line 3 of claim 14. There is insufficient antecedent basis for this limitation in the claim. It is suggested that the claim be amended to e.g. "the at least one signal component" to correct antecedent basis.

Claim 16 recites the limitation "the other oligonucleotide" in line 2. There is insufficient antecedent basis for this limitation in the claim. It is not clear if "the other oligonucleotide" is the same as the "another oligonucleotide" in Claim 14 or if "the other oligonucleotide" is an additional oligonucleotide" It is suggested that the claim be amended to e.g. "the another oligonucleotide" to correct antecedent basis.

Claim 17 is unclear because it is unclear where the several sequences are simultaneously amplified should be placed in the method of Claim 1. It is not clear if these sequences are amplified after detection because there is no step in Claim 1 which "amplifies".

Claim 18-20 are unclear because it seems to be limiting an amplification step of Claim 1, however, there are no amplification steps in Claim 1.

Claims 19-21 are indefinite over the phrase "primer bear " because it is unclear what the metes and bounds of the phrase "primer bear" encompasses. It is not clear how the primer "bear" two signal components or probes, if this phrase means the primer comprising two signal components the primers comprise a probe or some other undefined relationship.

Claims 22-28 are unclear over the phrase in the parentheses. The claims contain information in parentheses, i.e. ("methyl hairpin"), ("MSP methyl hairpin"), ("heavy methyl hairpin"), ("methyl duplex"), ("MSP methyl duplex"), ("heavy methyl duplex"), or ("quantitative methyl hairpin").. Parentheticals make the claim indefinite because it is unclear whether the information in the parentheses has the same, less, or more weight as the rest of the claim language.

Claims 29-30 provides for the use of the method of claim 1 or the use of scorpion primers for methylation analysis, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 29-30 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claims 22-24 are indefinite because it is unclear how each differs to further limit the parent. Each of these claims comprises the same steps however the preamble describes a different amplification process is taking place.

Claims 25-27 are indefinite because it is unclear how each differs to further limit the parent. Each of these claims comprises the same steps however the preamble describes a different amplification process is taking place.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-2 and 4-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eads et al. (Nucleic acids Research 2000 Vol. 28 p. e32) in view of Solinas et al. (Nucleic acids Research 2001 Vol. 29 p. e96).

Eads et al. teaches a method for detecting of cytosine methylation (abstract).

With regard to Claim 1 step a, Eads et al. teaches reacting the DNA with a chemical (e.g. sodium bisulfite) to change unmethylated cytosine to uracil (p. ii 1st column last full sentence). With regard to Claim 1 step b, Eads et al. teaches a PCR amplification with a polymerase, at least one primer, and a probe (p ii 2nd column Methylight primer and probe sequences and Figure 1). However, Eads et al. does not teaches that the primer is joined with a probe via a linker. With regard to Claim 1 step c-e, Eads et al. teaches separating the primer strand and detection whether or not hybridization of the probe has occurred (figure 1).

With regard to Claim 2, Eads et al. teaches reacting the DNA with sodium bisulfite (p. ii 1st column last full sentence).

With regard to Claims 4-5, Eads et al. teaches a method of MSP RT-PCR (p. ii 1st column last paragraph and 2nd column 1st paragraph).

With regard to Claim 6, Eads et al. teaches a probe that has two signal components that are proximity to one another (p. ii 2nd column 2nd paragraph).

With regard to Claim 7, Eads et al. teaches quencher-florescent dye pair (p. ii 2nd column 2nd paragraph).

With regard to Claim 17, Eads et al. teaches that several sequences are simultaneously amplified(p. ii 2nd column 2nd and 3rd paragraphs).

With regard to Claim 29, Eads et al teaches a method of using for diagnosing mismatching in genes associated with cancer disorders (abstract).

However, Eads et al. does not teaches that the primer is joined with a probe via a linker.

Solinas et al. teaches using Scorpion primers in PCR assays (abstract). With regard to Claim 1, Solinas et al. teaches a primer whose 5' end is joined with a probe via a linker (e.g. Scorpion primer) (Figure 1).

With regard to Claim 8, Solinas et al. teaches the probe forms a hairpin shape (p. 1 2nd column 1st paragraph).

With regard to Claim 9, Solinas et al. teaches the probe bears two signal components separated in the inactive form and activated after hybridization (Figure 1A).

With regard to Claim 10, Solinas et al. teaches detecting the signal using FRET (p. 3 1st column 1st paragraph).

With regard to Claim 11, Solinas et al. teaches a duplex Scorpion format wherein there is a signal on the probe and a signal on another oligonucleotide (Figure 1B).

With regard to Claim 12, Solinas et al. teaches detecting the signal using FRET (p. 3 1st column 1st paragraph).

With regard to Claim 13, Solinas et al. teaches a duplex Scorpion format wherein there is a signal on the probe and a signal on another oligonucleotide thereby separating the signals in the inactive form (Figure 1B).

With regard to Claim 14, Solinas et al. teaches a method wherein the probe comprises a signal and the other oligonucleotide bears a signal and under hybridization there is a signal (Figure 1b).

With regard to Claim 15, Solinas et al. teaches detecting the signal using FRET (p. 3 1st column 1st paragraph).

With regard to Claim 16 Solinas et al. teaches the another binder binds in immediate proximity to the probe (Figure 1B).

With regard to Claim 18, Solinas et al. teaches that two scorpion primers can be used (Table 2).

With regard to Claim 19, Solinas et al. teaches that each Scorpion primer has a different signal (Table 2).

With regard to Claims 20, 21, and 28, Solinas et al. teaches Scorpion primers can be used to detect differences in nucleic acid structure (abstract). It would be obvious to design Scorpion primers to detect methylation and nonmethylated areas of the nucleic acid to use the primers in the methylation assay of Eads et al. Eads et al. teaches designing probes which hybridize to methylated and nonmethylated nucleic acid structures (Figure 1 of Eads et al.).

With regard to Claims 22-24, Solinas et al. teaches a probe with a quencher and a dye molecule which are in the inactive form when in spatial proximity (e.g. hairpin form) and are activated by hybridization of the probe to a primer extension product (Figure 1A).

With regard to Claims 25-27, Solinas et al teaches an assay wherein the probe comprises a dye molecular and another oligonucleotides comprises a quencher and when the two are close they are inactive but after hybridization they are active (e.g. a duplex) (Figure 1B).

With regard to Claim 30, Solinas et al. teaches a method of using Scorpion primers to detect differences in tissues (abstract).

Therefore it would have been prime facie obvious to one of ordinary skill in the art to modify the methylation method of Eads et al. to include Scorpion primers linked to probes as taught by Solinas et al. The ordinary artisan would be motivated to modify the methylation method of Eads et al. to include Scorpion primers linked to probes as taught by Solinas et al., because Solinas et al. teaches the use of Scorpion primers in PCR assays allows an intermolecular probe-target interaction which results in a very fast and reliable detection system (p. 1 2nd column 2nd paragraph). Therefore the ordinary artisan would be motivated to use Scorpion primers to detect methylation and nonmethylation sites fast and reliably.

7. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Eads et al. (Nucleic acids Research 2000 Vol. 28 p. e32) in view of Solinas et al. (Nucleic acids Research 2001 Vol. 29 p. e96) as applied to Claims 1-2 and 4-30 and in further view of Berlin et al. (US Patent Application Publication 2006/0183128 August 17, 2006).

The combination of Eads et al. and Solinas et al. teaches a method for detection of cytosine methylations in DNA, however, Eads et al. and Solinas et al. do not teach the addition of cytidine deaminase.

Berlin et al. teaches a method of DNA methylation. With regard to Claim 3, Berlin et al. teaches cytidine deaminase to use in methylation reaction (paragraph 166 p 17).

Therefore it would have been prime facie obvious to one of ordinary skill in the art to modify the methylation method of Eads et al. and Solinas et al. to include the reaction of cytidine deaminase as taught by Berlin et al. The ordinary artisan would be motivated to modify the methylation method of Eads et al. and Solinas et al. to include a reaction step with cytidine deaminase because Berlin et al. teaches that cytidine deaminase will convert cytosine bases which are unmethylatated at the 5' position to uracil to differentiate between methylated and unmethylated cytosine bases (paragraph 166 p. 17). The ordinary artisan would be motivated to treat the DNA with cytidine deaminase such that there is a detectable difference between methylated and unmethylated cytosine bases.

8. Claims 1-2, 4-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Distler et al. (US Patent Application 2004/0265814) in view of Solinas et al. (Nucleic acids Research 2001 Vol. 29 p. e96)

Distler et al. teaches a method for detecting of cytosine methylation (abstract).

With regard to Claim 1, Distler et al. teaches reacting the DNA with a chemical (e.g. sodium bisulfite) to change unmethylated cytosine to uracil, amplifying with a PCR amplification with a polymerase, at least one primer, and a probe (p. 3 paragraphs 28-32). However, Distler et al. does not teaches that the primer is joined with a probe via a linker. With regard to Claim 1 step c-e, Distler et al. teaches separating the primer strand and detection whether or not hybridization of the probe has occurred (p. 3 paragraph 32).

With regard to Claim 2, Distler et al. teaches reacting the DNA with sodium bisulfite (p. 3 paragraph 29).

With regard to Claims 4-5, Distler et al. teaches a method of PCR (p. 3 paragraph 30).

With regard to Claim 17, Distler et al. teaches that several sequences are simultaneously amplified(p. 2 paragraph 18).

With regard to Claim 29, Distler et al teaches a method of using for diagnosing mismatching in genes associated with cancer disorders (p 4 paragraph 45).

However, Distler et al. does not teaches that the primer is joined with a probe via a linker.

Solinas et al. teaches using Scorpion primers in PCR assays (abstract). With regard to Claim 1, Solinas et al. teaches a primer whose 5' end is joined with a probe via a linker (e.g. Scorpion primer) (Figure 1).

With regard to Claim 8, Solinas et al. teaches the probe forms a hairpin shape (p. 1 2nd column 1st paragraph).

With regard to Claim 9, Solinas et al. teaches the probe bears two signal components separated in the inactive form and activated after hybridization (Figure 1A).

With regard to Claim 6-7 and10, Solinas et al. teaches detecting the signal using FRET (p. 3 1st column 1st paragraph).

With regard to Claim 11, Solinas et al. teaches a duplex Scorpion format wherein there is a signal on the probe and a signal on another oligonucleotide (Figure 1B).

With regard to Claim 12, Solinas et al. teaches detecting the signal using FRET (p. 3 1st column 1st paragraph).

With regard to Claim 13, Solinas et al. teaches a duplex Scorpion format wherein there is a signal on the probe and a signal on another oligonucleotide thereby separating the signals in the inactive form (Figure 1B).

With regard to Claim 14, Solinas et al. teaches a method wherein the probe comprises a signal and the other oligonucleotide bears a signal and under hybridization there is a signal (Figure 1b).

With regard to Claim 15, Solinas et al. teaches detecting the signal using FRET (p. 3 1st column 1st paragraph).

With regard to Claim 16 Solinas et al. teaches the another binder binds in immediate proximity to the probe (Figure 1B).

With regard to Claim 18, Solinas et al. teaches that two scorpion primers can be used (Table 2).

With regard to Claim 19, Solinas et al. teaches that each Scorpion primer has a different signal (Table 2).

With regard to Claims 20, 21, and 28, Solinas et al. teaches Scorpion primers can be used to detect differences in nucleic acid structure (abstract). It would be obvious to design Scorpion primers to detect methylation and nonmethylated areas of the nucleic acid to use the primers in the methylation assay of Eads et al. Eads et al. teaches designing probes which hybridize to methylated and nonmethylated nucleic acid structures (Figure 1 of Eads et al.).

With regard to Claims 22-24, Solinas et al. teaches a probe with a quencher and a dye molecule which are in the inactive form when in spatial proximity (e.g. hairpin form) and are activated by hybridization of the probe to a primer extension product (Figure 1A).

With regard to Claims 25-27, Solinas et al teaches an assay wherein the probe comprises a dye molecular and another oligonucleotides comprises a quencher and when the two are close they are inactive but after hybridization they are active (e.g. a duplex) (Figure 1B).

With regard to Claim 30, Solinas et al. teaches a method of using Scorpion primers to detect differences in tissues (abstract).

Therefore it would have been prime facie obvious to one of ordinary skill in the art to modify the methylation method of Distler et al. to include Scorpion primers linked to probes as taught by Solinas et al. The ordinary artisan would be motivated to modify the methylation method of Distler et al. to include Scorpion primers linked to probes as taught by Solinas et al., because Solinas et al. teaches the use of Scorpion primers in PCR assays allows an intermolecular probe-target interaction which results in a very fast and reliable detection system (p. 1 2nd column 2nd paragraph). Therefore the ordinary artisan would be motivated to use Scorpion primers to detect methylation and nonmethylation sites fast and reliably.

9. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Distler et al. (US Patent Application 2004/0265814) in view of Solinas et al. (Nucleic acids Research 2001 Vol. 29 p. e96) as applied to Claims 1-2 and 4-30 and in further view of Berlin et al. (US Patent Application Publication 2006/0183128 August 17, 2006).

The combination of Distler et al. and Solinas et al. teaches a method for detection of cytosine methylations in DNA, however, Distler et al. and Solinas et al. do not teach the addition of cytidine deaminase.

Berlin et al. teaches a method of DNA methylation. With regard to Claim 3, Berlin et al. teaches cytidine deaminase to use in methylation reaction (paragraph 166 p 17).

Therefore it would have been prime facie obvious to one of ordinary skill in the art to modify the methylation method of Distler et al. and Solinas et al. to include the reaction of cytidine deaminase as taught by Berlin et al. The ordinary artisan would be motivated to modify the methylation method of Distler et al. and Solinas et al. to include a reaction step with cytidine deaminase because Berlin et al. teaches that cytidine deaminase will convert cytosine bases which are unmethylatated at the 5' position to uracil to differentiate between methylated and unmethylated cytosine bases (paragraph 166 p. 17). The ordinary artisan would be motivated to treat the DNA with cytidine deaminase such that there is a detectable difference between methylated and unmethylated cytosine bases.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1-30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-4, 15-16,18 of copending Application No. 11716207 in view of Solinas et al. (Nucleic acids Research 2001 Vol. 29 p. e96).

Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1,4,5-6, and 29 of the instant application is drawn to detecting cytosine methylation in DNA comprising reacting with a chemical or an enzyme, amplifying with a polymerase and at least one primer, separating the extension, and detecting the hybridization. Claim 1-3 and 18 of application no. 11716207 is drawn to the same method steps however, application 11716207 does not claim that the primer is joined with a probe via a linker.

Claims 2-3 of the instant application and Claim 16 of application no. 11716207 are both drawn to bisulfite reagent.

Claim 7 of the instant application and Claim 15 of application no. 11716207 are drawn to quencher fluorescent dye pairs.

Claim 17 of the instant application and Claim 4 of application no. 11716207 are both drawn to simultaneously amplify.

Application 11716207 does not claim that the primer is joined with a probe via a linker.

Solinas et al. teaches using Scorpion primers in PCR assays (abstract). With regard to Claim 1, Solinas et al. teaches a primer whose 5' end is joined with a probe via a linker (e.g. Scorpion primer) (Figure 1).

With regard to Claim 8, Solinas et al. teaches the probe forms a hairpin shape (p. 1 2nd column 1st paragraph).

With regard to Claim 9, Solinas et al. teaches the probe bears two signal components separated in the inactive form and activated after hybridization (Figure 1A).

With regard to Claim 10, Solinas et al. teaches detecting the signal using FRET (p. 3 1st column 1st paragraph).

With regard to Claim 11, Solinas et al. teaches a duplex Scorpion format wherein there is a signal on the probe and a signal on another oligonucleotide (Figure 1B).

With regard to Claim 12, Solinas et al. teaches detecting the signal using FRET (p. 3 1st column 1st paragraph).

With regard to Claim 13, Solinas et al. teaches a duplex Scorpion format wherein there is a signal on the probe and a signal on another oligonucleotide thereby separating the signals in the inactive form (Figure 1B).

With regard to Claim 14, Solinas et al. teaches a method wherein the probe comprises a signal and the other oligonucleotide bears a signal and under hybridization there is a signal (Figure 1b).

With regard to Claim 15, Solinas et al. teaches detecting the signal using FRET (p. 3 1st column 1st paragraph).

With regard to Claim 16 Solinas et al. teaches another binder binds in immediate proximity to the probe (Figure 1B).

With regard to Claim 18, Solinas et al. teaches that two scorpion primers can be used (Table 2).

With regard to Claim 19, Solinas et al. teaches that each Scorpion primer has a different signal (Table 2).

With regard to Claims 20, 21, and 28, Solinas et al. teaches Scorpion primers can be used to detect differences in nucleic acid structure (abstract). It would be obvious to design Scorpion primers to detect methylation and nonmethylated areas of the nucleic acid to use the primers in the methylation assay of Eads et al. Eads et al. teaches designing probes which hybridize to methylated and nonmethylated nucleic acid structures (Figure 1 of Eads et al.).

With regard to Claims 22-24, Solinas et al. teaches a probe with a quencher and a dye molecule which are in the inactive form when in spatial proximity (e.g. hairpin form) and are activated by hybridization of the probe to a primer extension product (Figure 1A).

With regard to Claims 25-27, Solinas et al teaches an assay wherein the probe comprises a dye molecular and another oligonucleotides comprises a quencher and when the two are close they are inactive but after hybridization they are active (e.g. a duplex) (Figure 1B).

With regard to Claim 30, Solinas et al. teaches a method of using Scorpion primers to detect differences in tissues (abstract).

Therefore it would have been prime facie obvious to one of ordinary skill in the art to modify the methylation method of application 11716207 to include Scorpion primers linked to probes as taught by Solinas et al. The ordinary artisan would be motivated to modify the methylation method of application 11716207 to include Scorpion primers linked to probes as taught by Solinas et al., because Solinas et al. teaches the use of Scorpion primers in PCR assays allows an intermolecular probe-target interaction which results in a very fast and reliable detection system (p. 1 2nd column 2nd paragraph). Therefore the ordinary artisan would be motivated to use Scorpion primers to detect methylation and nonmethylation sites fast and reliably.

Accordingly, the claims of application 11716207 and the claims of the instant application are coextensive in scope and not patentably distinct form each other.

This is a provisional obviousness-type double patenting rejection.

12. Claims 1-2, 4-30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-2,11,14,18-19, and 27 of copending Application No. 10482433 in view of Solinas et al. (Nucleic acids Research 2001 Vol. 29 p. e96).

Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claims 1,4,5-6, and 29 of the instant application is drawn to detecting cytosine methylation in DNA comprising reacting with a chemical or an enzyme, amplifying with a polymerase and at least one primer, separating the extension, and detecting the

hybridization. Claim 1-2, 27 of application no. 10482433 is drawn to the same method steps however, application 10482433 does not claim that the primer is joined with a probe via a linker.

Claims 2 of the instant application and Claim 11 of application no. 10482433 are both drawn to bisulfite reagent.

Claim 7 of the instant application and Claim 18-19 of application no. 10482433 are drawn to quencher fluorescent dye pairs.

Claim 17 of the instant application and Claim 14 of application no. 10482433 are both drawn to simultaneously amplify.

Application 10482433 does not claim that the primer is joined with a probe via a linker.

Solinas et al. teaches using Scorpion primers in PCR assays (abstract). With regard to Claim 1, Solinas et al. teaches a primer whose 5' end is joined with a probe via a linker (e.g. Scorpion primer) (Figure 1).

With regard to Claim 8, Solinas et al. teaches the probe forms a hairpin shape (p. 1 2nd column 1st paragraph).

With regard to Claim 9, Solinas et al. teaches the probe bears two signal components separated in the inactive form and activated after hybridization (Figure 1A).

With regard to Claim 10, Solinas et al. teaches detecting the signal using FRET (p. 3 1st column 1st paragraph).

With regard to Claim 11, Solinas et al. teaches a duplex Scorpion format wherein there is a signal on the probe and a signal on another oligonucleotide (Figure 1B).

With regard to Claim 12, Solinas et al. teaches detecting the signal using FRET (p. 3 1st column 1st paragraph).

With regard to Claim 13, Solinas et al. teaches a duplex Scorpion format wherein there is a signal on the probe and a signal on another oligonucleotide thereby separating the signals in the inactive form (Figure 1B).

With regard to Claim 14, Solinas et al. teaches a method wherein the probe comprises a signal and the other oligonucleotide bears a signal and under hybridization there is a signal (Figure 1b).

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With regard to Claims 25-27, Solinas et al teaches an assay wherein the probe comprises a dye molecular and another oligonucleotides comprises a quencher and when the two are close they are inactive but after hybridization they are active (e.g. a duplex) (Figure 1B).

With regard to Claim 30, Solinas et al. teaches a method of using Scorpion primers to detect differences in tissues (abstract).

Therefore it would have been prime facie obvious to one of ordinary skill in the art to modify the methylation method of application 10482433 to include Scorpion primers linked to probes as taught by Solinas et al. The ordinary artisan would be motivated to modify the methylation method of application 10482433 to include Scorpion primers linked to probes as taught by Solinas et al., because Solinas et al. teaches the use of Scorpion primers in PCR assays allows an intermolecular probe-target interaction which results in a very fast and reliable detection system (p. 1 2nd column 2nd paragraph). Therefore the ordinary artisan would be motivated to use Scorpion primers to detect methylation and nonmethylation sites fast and reliably.

Accordingly, the claims of application 10482433 and the claims of the instant application are coextensive in scope and not patentably distinct form each other.

This is a provisional obviousness-type double patenting rejection.

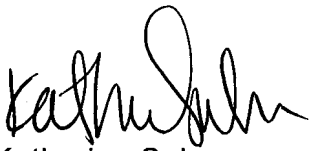
Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Katherine Salmon
Examiner

Art Unit 1634

/Jehanne Sitton/

Primary Examiner

11/23/2007